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Attorney Docket No. P67751US1  
Application No. 10/508,343**Amendments to the claims:**

This listing of claims replaces all prior versions, and listings, of claims in the application.

**Listing of claims:**

- 1 (original/withdrawn): A method of diagnosing or prognosticating a neurodegenerative disease in a subject, or determining whether a subject is at increased risk of developing said disease, comprising:

determining a level and/or an activity of

(i) a transcription product of a gene coding for human MAGUIN-1 and/or human MAGUIN-2, and/or

(ii) a translation product of a gene coding for human MAGUIN-1 and/or human MAGUIN-2, and/or

(iii) a fragment, or derivative, or variant of said transcription or translation product, in a sample from said subject and comparing said level and/or said activity to a reference value representing a known disease or health status, thereby diagnosing or prognosticating said neurodegenerative disease in said subject, or determining whether said subject is at increased risk of developing said neurodegenerative disease.

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- 2 (original/withdrawn): A method of monitoring the progression of a neurodegenerative disease in a subject, comprising:

determining a level and/or an activity of

(i) a transcription product of a gene coding for human MAGUIN-1 and/or human MAGUIN-2, and/or

(ii) a translation product of a gene coding for human MAGUIN-1 and/or human MAGUIN-2, and/or

(iii) a fragment, or derivative, or variant of said transcription or translation product, in a sample from said subject and comparing said level and/or said activity to a reference value representing a known disease or health status, thereby monitoring the progression of said neurodegenerative disease in said subject.

- 3 (original/withdrawn): A method of evaluating a treatment for a neurodegenerative disease, comprising: determining a level and/or an activity of

(i) a transcription product of a gene coding for human MAGUIN-1 and/or human MAGUIN-2, and/or

(ii) a translation product of a gene coding for human MAGUIN-1 and/or human MAGUIN-2, and/or

(iii) a fragment, or derivative, or variant of said transcription or translation product, in a sample from a subject being treated for said disease and comparing said level and/or

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said activity to a reference value representing a known disease or health status, thereby evaluating said treatment for said neurodegenerative disease.

- 4 (previously presented/withdrawn): The method according to claim 1 wherein said neurodegenerative disease is Alzheimer's disease.
- 5 (previously presented/withdrawn): The method according to claim 1 wherein said sample is a cell, or a tissue, or a body fluid, in particular cerebrospinal fluid or blood.
- 6 (previously presented/withdrawn): The method according to claim 1 wherein said reference value is that of a level and/or an activity of
  - (i) a transcription product of a gene coding for human MAGUIN-1 and/or human MAGUIN-2, and/or
  - (ii) a translation product of a gene coding for human MAGUIN-1 and/or human MAGUIN-2, and/or
  - (iii) a fragment, or derivative, or variant of said transcription or translation product, in a sample from a subject not suffering from said neurodegenerative disease.
- 7 (previously presented/withdrawn): The method according to claim 1 wherein an alteration in the level and/or activity of a transcription product of the gene coding for human MAGUIN-1 and/or

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human MAGUIN-2 and/or a translation product of the gene coding for human MAGUIN-1 and/or human MAGUIN-2 and/or a fragment, or derivative, or variant thereof, in a sample cell, or tissue, or body fluid, in particular cerebrospinal fluid, from said subject relative to a reference value representing a known health status indicates a diagnosis, or prognosis, or increased risk of Alzheimer's disease in said subject.

- 8 (previously presented/withdrawn): The method according to claim 1, further comprising:  
comparing a level and/or an activity of
- (i) a transcription product of a gene coding for human MAGUIN-1 and/or human MAGUIN-2, and/or
  - (ii) a translation product of a gene coding for human MAGUIN-1 and/or human MAGUIN-2, and/or
  - (iii) a fragment, or derivative, or variant of said transcription or translation product, in a series of samples taken from said subject over a period of time.
- 9 (original/withdrawn): The method according to claim 8, wherein said subject receives a treatment prior to one or more of said sample gatherings.
- 10 (original/withdrawn): The method according to claim 9 wherein said level and/or activity is determined before and after said treatment of said subject.

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11 (original/withdrawn): A kit for diagnosing or prognosticating a neurodegenerative disease, in particular Alzheimer's disease, in a subject, or determining the propensity or predisposition of a subject to develop such a disease, said kit comprising:

- (a) at least one reagent which is selected from the group consisting of
  - (i) reagents that selectively detect a transcription product of a gene coding for human MAGUIN-1 and/or human MAGUIN-2, and
  - (ii) reagents that selectively detect a translation product of a gene coding for human MAGUIN-1 and/or human MAGUIN-2 and
- (b) an instruction for diagnosing or prognosticating a neurodegenerative disease, in particular Alzheimer's disease, or determining the propensity or predisposition of a subject to develop such a disease by
  - (i) detecting a level, or an activity, or both said level and said activity, of said transcription product and/or said translation product of a gene coding for human MAGUIN-1 and/or human MAGUIN-2 in a sample from said subject; and
  - (ii) diagnosing or prognosticating a neurodegenerative disease, in particular Alzheimer's disease, or determining the propensity or predisposition of said subject to develop such a disease, wherein a varied level, or activity, or both said level and said activity, of said transcription product and/or said translation product compared to a reference value representing a known health status; or a level, or activity, or both said level and said activity, of said transcription product and/or said translation product similar or equal to

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a reference value representing a known disease status indicates a diagnosis or prognosis of a neurodegenerative disease, in particular Alzheimer's disease, or an increased propensity or predisposition of developing such a disease.

12 (original/withdrawn): A method of treating or preventing a neurodegenerative disease, in particular Alzheimer's disease, in a subject comprising administering to said subject in a therapeutically or prophylactically effective amount an agent or agents which directly or indirectly affect an activity and/or a level of (i) a gene coding for human MAGUIN-1 and/or human MAGUIN-2, and/or (ii) a transcription product of a gene coding for human MAGUIN-1 and/or human MAGUIN-2, and/or (iii) a translation product of a gene coding for human MAGUIN-1 and/or human MAGUIN-2, and/or (iv) a fragment, or derivative, or variant of (i) to (iii).

13 (original/withdrawn): A modulator of an activity and/or of a level of at least one substance which is selected from the group consisting of (i) a gene coding for human MAGUIN-1 and/or human MAGUIN-2, and/or (ii) a transcription product of a gene coding for human MAGUIN-1 and/or human MAGUIN-2, and/or (iii) a translation product of a gene coding for human MAGUIN-1 and/or human MAGUIN-2, and/or (iv) a fragment, or derivative, or variant of (i) to (iii).

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14 (original/withdrawn): A pharmaceutical composition comprising a modulator according to claim 13.

15 (original/withdrawn): Use of a modulator of an activity and/or of a level of at least one substance which is selected from the group consisting of (i) a gene coding for human MAGUIN-1 and/or human MAGUIN-2, and/or (ii) a transcription product of a gene coding for human MAGUIN-1 and/or human MAGUIN-2, and/or (iii) a translation product of a gene coding for human MAGUIN-1 and/or human MAGUIN-2, and/or (iv) a fragment, or derivative, or variant of (i) to (iii) for a preparation of a medicament for treating or preventing a neurodegenerative disease, in particular Alzheimer's disease.

16 (original/withdrawn): A recombinant, non-human animal comprising a non-native gene sequence coding for human MAGUIN-1 and/or human MAGUIN-2 or a fragment, or a derivative, or a variant thereof, said animal being obtainable by:

- (i) providing a gene targeting construct comprising said gene sequence and a selectable marker sequence, and
- (ii) introducing said targeting construct into a stem cell of a non-human animal, and
- (iii) introducing said non-human animal stem cell into a non-human embryo, and
- (iv) transplanting said embryo into a pseudopregnant non-human animal, and
- (v) allowing said embryo to develop to term, and

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- (vi) identifying a genetically altered non-human animal whose genome comprises a modification of said gene sequence in both alleles, and
- (vii) breeding the genetically altered non-human animal of step
- (vi) to obtain a genetically altered non-human animal whose genome comprises a modification of said endogenous gene, wherein said disruption results in said non-human animal exhibiting a predisposition to developing symptoms of a neurodegenerative disease or related diseases or disorders.

17 (original/withdrawn): Use of the recombinant, non-human animal according to claim 16 for screening, testing, and validating compounds, agents, and modulators in the development of diagnostics and therapeutics to treat neurodegenerative diseases, in particular Alzheimer's disease.

Claims 18-20 (cancelled).

21 (original/withdrawn): A method for producing a medicament comprising the steps of (i) identifying a modulator of neurodegenerative diseases, in particular Alzheimer's disease, by a method according to claim 18 and (ii) admixing the modulator with a pharmaceutical carrier.



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- 22 (original/withdrawn): A method for producing a medicament comprising the steps of (i) identifying a compound as an inhibitor of binding between a ligand and a human MAGUIN-1 and/or human MAGUIN-2 gene product by a method according to claim 19 and (ii) admixing the compound with a pharmaceutical carrier.
- 23 (original/withdrawn): A method for producing a medicament comprising the steps of (i) identifying a compound as a binder to a human MAGUIN-1 and/or human MAGUIN-2 gene product by a method according to claim 20 and (ii) admixing the compound with a pharmaceutical carrier.
- 24 (original/withdrawn): A medicament obtainable by any of the methods according to claim 21.
- 25 (original/withdrawn): A medicament obtained by any of the methods according to claim 21.
- 26 (original/withdrawn): A protein molecule shown in SEQ ID NO.1 or SEQ ID NO.2, or a fragment, or derivative, or variant thereof, for use as a diagnostic target for detecting a neurodegenerative disease, preferably Alzheimer's disease.
- 27 (original/withdrawn): A protein molecule shown in SEQ ID NO. 1 or SEQ ID NO.2, or a fragment, or derivative, or variant thereof, for use as a screening target for reagents or

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compounds preventing, or treating, or ameliorating a neurodegenerative disease, preferably Alzheimer's disease.

- 28 (original/withdrawn): An antibody specifically immunoreactive with an immunogen, wherein said immunogen is a protein molecule shown in SEQ ID NO. 1, or a fragment, or derivative, or variant thereof.
- 29 (original/withdrawn): An antibody specifically immunoreactive with an immunogen, wherein said immunogen is a protein molecule shown in SEQ ID NO. 2, or a fragment, or derivative, or variant thereof.
- 30 (previously presented/withdrawn): Use of an antibody of claim 28, for detecting the pathological state of a cell in a sample from a subject, comprising immunocytochemical staining of said cell with said antibody, wherein an altered degree of staining, or an altered staining pattern in said cell compared to a cell representing a known health status indicates a pathological state of said cell.
- 31 (new): An assay for screening candidate compounds for a modulator of Alzheimer's disease comprising the steps of:
- a) contacting a test cell with a test compound;

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- b) measuring the activity and/or level of one or more substances selected from the group consisting of
    - i) a gene coding for human MAGUIN-1 (SEQ ID NO: 1) and/or human MAGUIN-2 (SEQ ID NO: 2), and/or
    - ii) a transcription product of a gene coding for human MAGUIN-1 and/or human MAGUIN-2, and/or
    - iii) a translation product of a gene coding for human MAGUIN-1 and/or human MAGUIN-2;
  - c) measuring the activity and/or level of the one or more substances in a control cell not contacted with the test compound; and
  - d) comparing the measured activity and/or level in the test cell with the measured activity and/or level in the control cell, wherein an alteration between (A) the measured activity and/or level in the test cell and (B) the measured activity and/or level in the control cell indicates that the test compound is a modulator of Alzheimer's disease.
- 32 (new): A method of testing one or more compounds, for inhibition of binding between a ligand and human MAGUIN-1 (SEQ ID NO: 1) and/or human MAGUIN-2 (SEQ ID NO: 2), the method comprising the steps of:
- a) adding a liquid suspension of the human MAGUIN-1 and/or human MAGUIN-2 to a plurality of containers;

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- b) adding one or more compounds, to be screened for the inhibition of binding, to the plurality of containers;
- c) adding a detectable ligand to the containers;
- d) incubating the liquid suspension of the human MAGUIN-1 and/or human MAGUIN-2, with the one or more compounds and the ligand;
- e) measuring amounts of detectable ligand associated with the human MAGUIN-1 and/or human MAGUIN-2; and
- f) determining the degree of inhibition, by the one or more compounds, of binding of the ligand to the human MAGUIN-1 and/or human MAGUIN-2.

33 (new): The method of of claim 32 wherein the detectable ligand is a fluorescently detectable ligand.

34 (new): A method of testing one or more compounds, to determine the degree of binding of the one or more compounds to human MAGUIN-1 (SEQ ID NO: 1) and/or human MAGUIN-2 (SEQ ID NO: 2), the method comprising the steps of:

- a) adding a liquid suspension of the human MAGUIN-1 and/or human MAGUIN-2 to a plurality of containers;
- b) adding one or more detectable compounds to be screened for binding to the plurality of containers;

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- c) incubating the liquid suspension of the human MAGUIN-1 and/or human MAGUIN-2 with the one or more detectable compounds;
- d) measuring amounts of the one or more detectable compounds associated with the human MAGUIN-1 and/or human MAGUIN-2; and
- e) determining the degree of binding by the one or more detectable compounds to the human MAGUIN-1 and/or human MAGUIN-2.

35 (new): The method of of claim 34 wherein the one or more detectable compounds is one or more fluorescently detectable compounds.